MILITARY BENEFIT

DEPARTMENT OF DEFENSE
Neurofibromatosis Research Program

Neurofibromatosis (NF) Research offers insight into many diseases, and the Department of Defense NF Research Program (NFRP) is providing critical research support that is of benefit to the military and the general population. Below are examples of recently funded NFRP research that could have a broad impact for those with NF, as well as the military.

- **Pain**
- **Cancer**
- **Hearing Loss and Deafness**
- **Mental Health**
- **Bone Repair**

- **Neurofibromatosis (NF) is a group of genetic disorders that cause widespread, severe medical illness.** This includes tumors of brain, nerves, skin, breasts; deafness; blindness; paralysis; cognitive disabilities; unmanageable chronic pain; bone abnormalities; psychosocial issues; and cardiovascular defects.

- **Anyone can be affected by NF.** There are three forms of NF: NF1, NF2 and schwannomatosis. Together, these affect 1 in 3000 people. Half of NF cases are inherited from a parent, but half occur sporadically due to random genetic mutation during development. This means that NF may affect any person from any family.

- **NF research can benefit the military as a model for advancing treatments for many relevant conditions.** The same genes that are mutated in NF are often mutated in diseased tissues in people who *don't* have NF. Further, the proteins made by those NF genes play key roles in many normal body processes. Drugs that restore normal NF-associated cellular function are being developed to treat the manifestations of NF but may also help people *without* NF who are suffering from various conditions including diseases of nerve, brain, bone, breast, blood vessels, or even pain.

- **The Department of Defense fills a special role by providing peer-reviewed funding for cutting-edge medical research through the Congressionally Directed Medical Research Program (CDMRP).** The well-executed and efficient programs within the CDMRP, including the NFRP, demonstrate responsible stewardship of taxpayer dollars.

- **NFRP grants do not duplicate or supplant NIH research efforts, but rather enhance and complement NIH efforts.** Research grants are awarded in every state in the country through a competitive two-tier review process.

Pain

Pain is one of the most common and most troubling symptoms for patients with NF, as it is in both active duty and retired members of the military. Advances in the field of NF-associated pain may extend to benefit the military through better understanding of biology and discovery of two non-opioid therapeutics.

- **Dr. Rajesh Khanna** (*University of Arizona)* and colleagues used a pig model of NF1 to build on their prior rodent data showing that the CRMP2 protein plays a vital role in abnormal pain signaling in NF1. They determined that the pig model more closely resembles human NF1-associated pain than rodents and were able to reverse abnormally increased nerve cell signaling with two novel therapeutic compounds. This work not only advanced our understanding of the molecular basis for pain in NF1, but more importantly it identified two non-opioid treatments that improved pain in various rodent and pig models. This confirmed previous rodent data, and further suggested a new therapeutic target for the treatment of pain.

Mental Health

Nearly 80% of patients with NF1 suffer from some form of psychosocial or cognitive disability, including learning disabilities, attention deficit disorder, or autism-like features. Better understanding cognitive changes in NF1 may translate to major benefits for the military, including potential advances in post-injury cognitive changes in soldiers or in degenerative cognitive diseases in veterans. In addition, resiliency is the ability to maintain adaption and effective functioning amid challenges. NF research in resilience will help NF patients, military personnel and veterans to navigate health, and service-related experiences.

- **Dr. Jonathan Payne** (Murdoch Children's Research Institute, Australia) is using a special type of MRI, called magnetic resonance spectroscopy (MRS), to safely and non-invasively study the levels of the neurotransmitter GABA in the brains of children with NF1. GABA is a chemical that transmits messages between brain cells, and it has been implicated not only in learning disabilities in NF1, but also in Post-Traumatic Stress Disorder. Development of MRS technology to easily quantify GABA levels in the brain may help us identify people at highest risk of developing learning disorders, PTSD, or other psychosocial disabilities.

- **Dr. Ana-Maria Vranceanau** (*Massachusetts General Hospital)* and colleagues compared resiliency improvement through either a mind-body resiliency program or a general health education program delivered by online video-chat with captioning for patients deafened by NF2. Gratitude, mindfulness, perceived coping, and other measures were improved and sustained with mind-body resiliency training. This data adds to previously published work that online mind-body training promotes resiliency for all kinds of patients.

Cancer

Both NF1 and military service are associated with increased risks of certain cancers, including breast cancer and sarcomas. Therefore, discoveries involving the biology or treatment of NF1-associated cancers are relevant and important to military service members and veterans. In addition, many types of soft tissue sarcomas have been associated with exposure to herbicides containing dioxin (e.g. Agent Orange). Advancing our knowledge of the biology of Malignant Peripheral Nerve Sheath Tumors (MPNST) is likely to reveal new treatment strategies.

- **Dr. Margaret Wallace** (*University of Florida*) and colleagues identified recurrent losses of the genes *CDKN2A/B* and *SMARCA2* in atypical neurofibromas, and recurrent mutations and deletions of the genes *EED* and *SUZ12* within MPNSTs. Malignant Peripheral Nerve Sheath Tumors (MPNST) is a type of soft tissue sarcoma that may develop or may arise from malignant transformation of pre-existing benign nerve sheath tumors. This data suggests a series of key genetic events required for the transition from benign to atypical neurofibroma, and then to MPNST, and may provide therapeutic targets for future development.

- **Dr. Xia Wang** (Moffitt Cancer Center) identified that NF1-associated breast cancers have marked overexpression of the protein HER2 when extra copies of the ErbB2 gene are present. This suggests an important interplay between the NF1 gene and the ErbB2 gene in breast cancer development, and potentially an opportunity for therapeutic development since FDA-approved HER2-targeting drugs already exist.

Hearing Loss and Deafness

Vestibular schwannomas are a common, pathologically benign tumor, with more than 4% lifetime risk of development in the general population. There is increased risk of developing these tumors after exposure to radiation. These are also the most common tumor in NF2. Vestibular schwannomas may lead to hearing loss deafness, imbalance, or facial weakness.

- **Dr. Scott Plotkin** (*Massachusetts General Hospital*) and colleagues from the DOD-funded NF Clinical Trial Consortium determined that standard dose bevacizumab (an antibody therapy) is optimal for restoring hearing and shrinking tumors, while high dose bevacizumab provided no additional benefit. The preference for standard dose was further emphasized by biomarkers suggesting that high dose treatment overshoots a therapeutic window that is otherwise achieved by standard dose therapy. This will impact anyone receiving bevacizumab for vestibular schwannoma.

- **Dr. Wade Clapp** (*Indiana University*) and colleagues discovered that NF-κB is a driver of schwannoma development in cells with *NF2* loss, and that NF-κB signaling is promoted by alternative handling of the NIK protein, producing an NF-κB-activating fragment that cannot be removed through traditional cellular functions. Further study showed that blocking NIK signaling reduced tumor cell proliferation, while introduction of NIK to normal cells led to tumor-like behavior. Taken together, this suggests NIK is likely an important driver of schwannoma development and blocking it may be an effective therapy for these tumors.

Bone Repair

Skeletal abnormalities affect up to one-third of patients with NF1. Included among these is improper fracture healing that may lead to permanent bone damage and amputation. Research involving NF1-associated bone disease and healing is likely to be more broadly applicable, including to military-associated injuries.

- **Dr. Elizabeth Schorry** (*Cincinnati Children's Hospital*) and the entire Neurofibromatosis Clinical Trials Consortium, which is an NFRP funded entity, are presently conducting a clinical trial to accelerate bone healing after surgery for tibial fractures. Approximately 10% of children with NF1 have a propensity for repeated fractures and leg bone malformation (pseudoarthrosis), which often requires surgical repair or even amputation. BMP-2 is a naturally occurring human protein that induces bone cell growth in normal development and can now be re-created in a laboratory as rhBMP-2. This trial is evaluating whether application of rhBMP-2 to the surgical site for tibial fracture repairs may improve healing. This has a strong possibility of directly impacting orthopedic surgery for other indications, including trauma such as is seen in the military.